Hemodynamics for the Heart Failure Clinician: A State-of-the-Art Review

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ABSTRACT

Heart failure (HF) fundamentally reflects an inability of the heart to provide adequate blood flow to the body without incurring the cost of increased cardiac filling pressures. This failure occurs first during the stressed state, but progresses until hemodynamic derangements become apparent at rest. As such, the measurement and interpretation of both resting and stressed hemodynamics serve an integral role in the practice of the HF clinician. In this review, we discuss conceptual and technical best practices in the performance and interpretation of both resting and invasive exercise hemodynamic catheterization, relate important pathophysiologic concepts to clinical care, and discuss updated, evidence-based applications of hemodynamics as they pertain to the full spectrum of HF conditions. (*J Cardiac Fail 2022;28:133–148*)
Key Words: Hemodynamics, cardiac function, heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, cardiogenic shock, pulmonary hypertension.

In 1929, Dr Werner Forssmann conducted the first cardiac catheterization procedure—on himself—by advancing a urological tube from an antecubital vein to the right atrium, and in doing so, inaugurated a new era in cardiology. Forty years later, Swan and Ganz innovated a new pulmonary artery (PA) catheter feasible for use at the bedside, expanding use of hemodynamic assessments in the diagnosis and care of patients with cardiac disease. In subsequent years, advances in echocardiography and shifts in the cardiac catheterization laboratory from a diagnostic to therapeutic emphasis led to a decreased use of invasive hemodynamics. However, the past decade has witnessed a resurgence in the use of resting and exercise invasive hemodynamic assessments, which provide a powerful tool to identify and care for patients with heart failure (HF).[1,2]

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Manuscript received June 11, 2021; revised manuscript received July 19, 2021; revised manuscript accepted July 21, 2021.

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1071-9164/$ - see front matter

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https://doi.org/10.1016/j.cardfail.2021.07.012

In this review, we summarize the concepts and best practices in the performance and interpretation of hemodynamic assessments across the HF disease spectrum (Table 1).

Conceptual Principles

Pressure and Pressure–Volume Relationships

Pressure defines force applied to an area: 1 mm Hg represents the vertical force of 133.3 Newtons applied to an area of 1 m^2. Cardiac contractions expose the cardiovascular system to cyclic variations in pressure—greatest in the ventricles and lowest in the capillaries. Blood flow to support life is driven by the pressure gradients generated by the heart. During systole, ventricular and atrial pressures increase, increasing pressure to propel blood forward. During relaxation, pressure decays rapidly so that cardiac filling may occur as pressure decreases. During diastole, increases in chamber volume stretch elastic elements within the heart and pericardium to increase pressure. The magnitude of this pressure increase is related to the volume of blood distending the chamber, the viscoelastic properties of myocardial tissue, the velocity and extent of relaxation, and the amount of external restraint on the heart. Understanding pressure and pressure–volume concepts helps to contextualize the hemodynamic assessment, because hemodynamics measure pressure and flow but fail to capture volume.

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Table 1. Summary of Uses of Resting and Invasive Exercise Hemodynamics

Clinical Entity	Use of Resting RHC	Use of Invasive Exercise RHC
1. Exertional dyspnea	Evaluate for HF or PH; provocative maneuvers (eg, fluid) can improve sensitivity	Gold standard evaluation of exertional dyspnea
2. HFrEF	Assess hemodynamics when volume and perfusion status are unclear; guide therapy	Assess CO limitation to exertion
3. CS	Diagnosis and assessment; guide medical and mechanical circulatory support therapy	—
4. Advanced HF evaluation	Evaluate candidacy; vasodilator therapy to assess precapillary PH before transplant; assess risk of RHF after LVAD	Assess CO limitation to exertion; differentiate from poor peripheral reserve
5. Heart transplantation	Concurrent with endomyocardial biopsies to rule out allograft rejection	—
6. LVAD management	Assess for precapillary PH; help to diagnose LVAD complications; optimize perfusion and filling pressures via ramp studies	May be a role for assessing adequacy of LVAD pump speed
7. HFpEF	Diagnosis; rule out cardiac amyloidosis via endomyocardial biopsy	Diagnosis when resting assessments remain unclear; assess CO limitation
8. PH	Gold standard evaluation; PH subtyping; vasodilator provocation in PAH	May be a role for diagnosis of exercise-induced PH
9. Valvular disease	Reconcile differences between clinical and noninvasive assessments	Assess for exertional exacerbation of valvular lesions
10. Congenital heart disease	Diagnose left-to-right shunts; assess PH; assess hemodynamics of complex lesions	Potential role in Fontan palliation to evaluate pulmonary vascular reserve
11. High-output HF	Diagnosis; ascertain shunt lesions	—
11. Preload reserve and peripheral limitations	—	Diagnosis
12. Pericardial disease	Diagnose constrictive versus restrictive process (with concomitant LHC)	Volume loading of exercise can sometimes help identify occult constriction

CO, cardiac output; CS, cardiogenic shock; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LHC, left heart catheterization; LVAD, left ventricular assist device; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization.

The pressure–volume loop of the left ventricle (LV) operates within the space subtended by the end-systolic pressure–volume relationship (ESPVR; also known as end-systolic elastance [Ees]) and the end-diastolic pressure–volume relationship (EDPVR), with the differences between the end-diastolic volume (EDV) (right) and end-systolic volume (left) defining the stroke volume (SV) (Fig. 1A). The ESPVR and EDPVR characterize, in a load-independent manner, ventricular contractile and diastolic compliance properties, respectively. In a patient with well-compensated HF with reduced ejection fraction (HFrEF), contractility is depressed, leading to a shallower ESPVR (Fig. 1B, top arrow), but the LV can still supply a near-normal SV at rest—and even maintain acceptable LV end-diastolic pressure (EDP)—because of an increase in LV volumes (bottom arrow).[3] Note that ejection fraction (EF) is depressed because the EDV increased, not because the SV decreased.

Afterload is indexed by effective arterial elastance (Ea), defined in the pressure–volume plane by the quotient of end-systolic pressure and SV (black diagonal). Ea reflects the lumped "stiffness" of the vasculature and is related directly to systemic vascular resistance and heart rate, and inversely related to arterial compliance.[3] The shallow ESPVR in HFrEF results in an increase in afterload-sensitivity.[4] Diuresis lowers LV EDV (Fig. 1A) which, in a hypervolemic patient with HFrEF with a steeper EDPVR, also decreases pressure and congestive symptoms. With decrease in the afterload, the Ea decreases (Fig. 1B, shallower slope, green), leading to a slight decrease in end-systolic pressure but marked improvement in SV. The opposite occurs with a vasoconstrictor (data not shown), which can markedly impair SV.

Inotropes and temporary mechanical circulatory support devices, used in low-output and cardiogenic shock (CS) states, also have distinct effects on the HFrEF LV pressure–volume loop.[3,5] Inotropes (eg, dobutamine and milrinone) augment the ESPVR while decreasing systemic vascular resistance; the net effect is an increased SV, decreased Ea, and decreased EDP (Fig. 1D).[3] These benefits, however, come at the cost of increased myocardial oxygen demand. Peripheral ventricular assist devices augment flow from LV to the systemic circulation. Intra-aortic balloon pump counterpulsation does so indirectly by decreasing systemic afterload during systole. For the LV with sufficient contractile reserve,[6] this practice can decrease the Ea, augment the SV, and decrease the LV EDV and EDP (Fig. 1E). Percutaneous microaxial flow pumps, which actively draw blood from the LV into the aorta, significantly decrease the LV filling pressures and myocardial demand (Fig. 1E) while dramatically augmenting systemic flow and mean arterial pressure (data not shown). Here, the triangular LV pressure–volume loop results from continuous LV emptying, which interrupts isovolumic contraction and relaxation. Of note, a durable left ventricular assist device (LVAD)

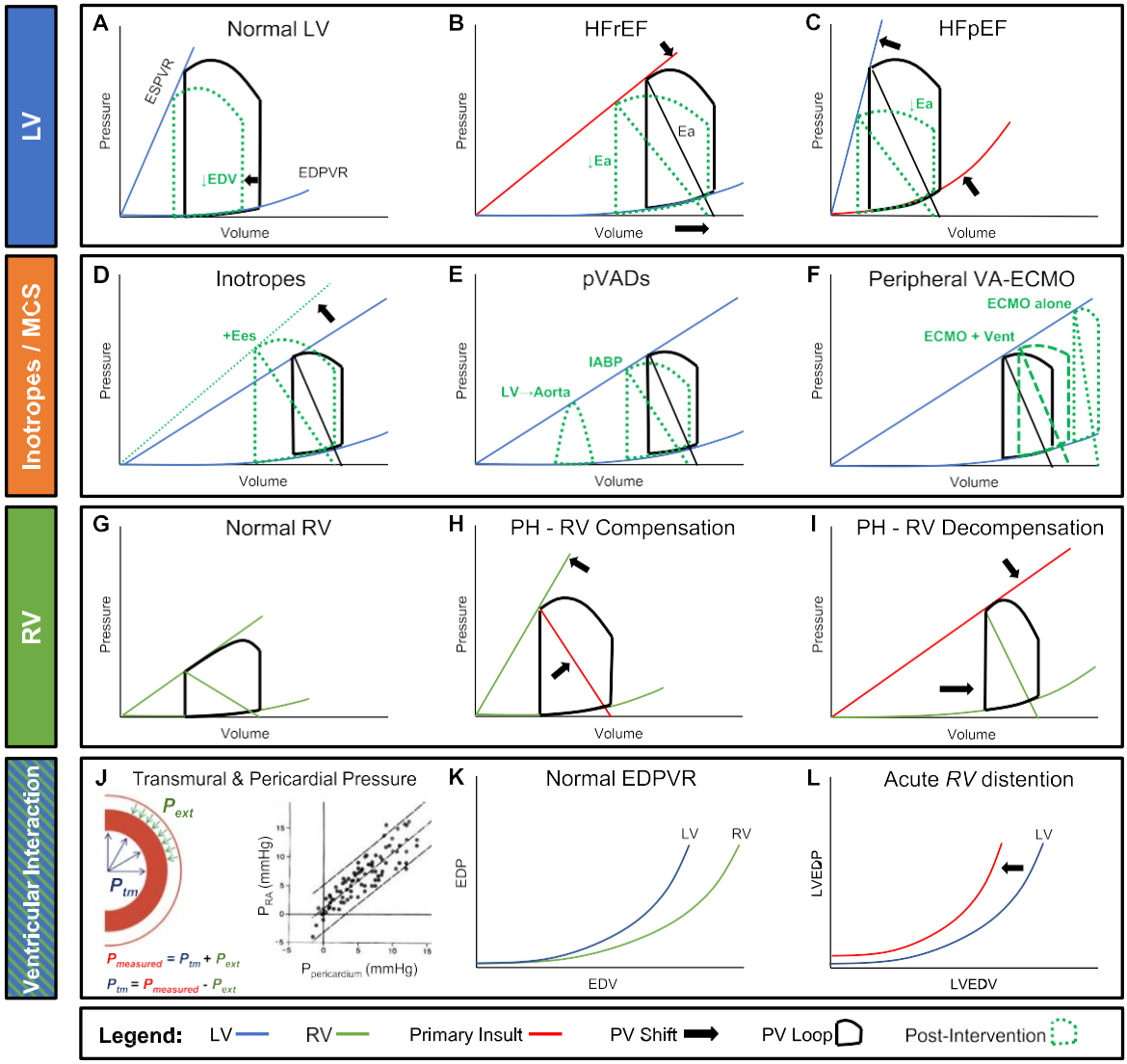

Fig. 1. Pressure–volume physiology of the left ventricle (LV), inotropes, and select mechanical circulatory support (MCS) devices, the right ventricle (RV), and ventricular–pericardial interactions. Key principles are thoroughly outlined in text. EDPVR, end-diastolic pressure–volume relationship; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PH, pulmonary hypertension; pVAD, percutaneous ventricular assist device; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

has a nearly identical effect on LV hemodynamics. Lastly, in extreme cases of CS, venoarterial-extracorporeal membrane oxygenation may be necessary to restore adequate flow and perfusion to the body. When done via peripheral cannulation, there is a significant afterload imposed against the ailing LV (Fig. 1F). In such cases, LV venting strategies, whether by pharmacologic or mechanical means (the latter is depicted in Fig. 1F), may be needed to mitigate the increased afterload, which in turn decreases the LV EDP to prevent pulmonary edema.

In patients with HF with preserved EF (HFpEF) there is commonly an EDPVR shift up and to the left, owing to increases in viscoelastic chamber stiffness (Fig. 1C). This factor results in higher filling pressures relative to chamber volume (bottom arrow), an effect that becomes amplified at higher volumes. In addition to active stiffening (ie, contractility), the ESPVR is increased through passive chamber stiffening, such that the ESPVR is increased in HFpEF, even as other measures of chamber and myocardial contractility are depressed[7] (upper arrow). Heightened systolic and diastolic stiffening render HFpEF patients highly sensitive to diuretics and vasodilators,[4,8] complicating management of both volume status and blood pressure (BP). With the same degree of afterload reduction (green), there is a much greater decrease in the BP, with less of an increase in SV in HFpEF as compared with HFrEF (Fig. 1C). Similarly, the increase in the EDPVR renders them more sensitive to LV preload reduction with venodilators, which can decrease the SV.[4]

The pulmonary circulation accepts the same cardiac output (CO) as the systemic circuit, but at one-fifth of the pressure. The RV pressure–volume loop differs from the LV in the amplitude of pressure change and generally takes a more trapezoidal or triangular shape (Fig. 1G). Like in the LV, the RV ESPVR slope (also termed the end-systolic elastance, or Ees) should match the Ea, resulting in an Ees/Ea ratio of greater than 1.0 in health.[9] In pulmonary hypertension (PH), the Ea increases as the PA pressure increases. When the RV is compensated, there is an accompanying increase in the Ees, maintaining the Ees/Ea ratio and EF (Fig. 1H). However, over time, patients with PH often progress to RV decompensation (Fig. 1I), where the RV Ees decreases relative to the Ea, the RV dilates to maintain SV, and the RV EF decreases. With progressive decompensation, the RV contractility and diastolic compliance worsen, the RV Ees/Ea decreases, the CO decreases, and the RV EDP and right atrial pressure (RAP) increase out of proportion to left-sided pressure. It can be difficult to ascertain when the compensated RV may be masking occult RV disease. In such patients, stressing the RV to reveal RV reserve may uncover RV pathology unapparent at rest.[10–12]

Finally, the pericardium also plays an important role in HF and PH. The RV and LV are connected in series, because the former provides flow to the latter. However, they may also influence one another in parallel, through the phenomenon of ventricular interaction, if the restraining effects of the pericardium amplify competition between the right and left heart for volume. Chamber or vascular pressure measured with a catheter represents the sum of transmural filling pressure (the forces from within favoring distention) together with the external pressure applied on the epicardium (that, when positive, opposes distention, Fig. 1J). In the heart, external pressure is equal to pericardial pressure, which can be estimated accurately by the RA pressure.[13] Under normal conditions, owing to its thicker walls, the LV has a steeper EDPVR than the RV (Fig. 1K), and pericardial restraint on the heart is minimal.[13] However, with acute increases in cardiac volume, as may accompany exercise, pulmonary embolism, or acute valve insufficiency, increases in pericardial restraint are augmented. The resulting increases in surface contact pressures on the epicardium transmit to increase intracavitary pressure, even as cardiac muscle properties remain unchanged. In other words, the intracavitary pressure is increased even if the transmural distending pressure is normal or even low, as often noted during acute decompensated HF (Fig. 1L). RV distention owing to central venous congestion shifts the LV EDPVR leftward by way of pericardial restraint. This factor in turn decreases the LV transmural filling pressure, decreasing the LV preload and thus CO (Fig. 1L).[13] In this situation, decongesting the RV with diuretics and venodilators is crucial to restoring LV transmural filling pressure and raising LV end-diastolic volume (true "preload").[13,14]

Hemodynamic Principles of Exercise Physiology

Resting hemodynamic abnormalities may be subtle or even absent during the early stages of HF or when patients are well-diuresed. In such cases, HF may only become evident during the stressed state, when the heart fails to respond to the heightened physiologic demands of exercise. According to the Fick principle, oxygen consumption (VO_2) is equal to the product of CO and the arteriovenous oxygen difference (AVO_2-diff). With physical exertion there is an increase in VO_2 that is achievable through combined increases in O_2 delivery (CO) and enhanced distribution and extraction of O_2 in skeletal muscle (increase in AVO_2-diff). In health, the CO increases at a ratio of 6 mL/min for every 1 mL/min increase in VO_2.[15] This increase is achieved through increases in heart rate and SV. The SV increases owing to enhanced venous return to augment preload, along with increases in contractility and decreases in vascular resistances in both the lungs and the systemic circulation to facilitate more complete ventricular ejection. The increase in venous return during exercise is related to the combined actions of skeletal muscle pumps and the venoconstriction in the large capacitance veins of the abdomen, increasing the stressed blood volume (the volume that contributes to increasing vascular pressure).[16]

At steady state, the venous return must equal the CO. During exercise, the heart must accommodate marked increases in blood return and flow without increasing filling pressures. This goal is achieved through biventricular lusitropic reserve, which allows both ventricles to fill to greater volumes despite a shorter diastolic time interval.[17] These adaptations enable a minimal increase in left the atrial pressure and RAP during exercise in healthy individuals,[18] which allows the pulmonary capillary and PA hydrostatic pressures to remain in the normal range.

Patients with HF may display limitations in each of these adaptations. Increases in arterial stiffness and inadequate vasodilation amplify LV afterload, contributing to pulmonary capillary wedge pressure (PCWP) increase.[19] LV and RV systolic reserve are impaired, limiting forward SV.[20] This combines with abnormalities in diastolic relaxation and compliance that further increase PCWP,[10,21] which then leads to increased fluid filtration across the pulmonary capillary–alveolar interface, resulting in the accumulation of extravascular lung water.[22] Chronotropic

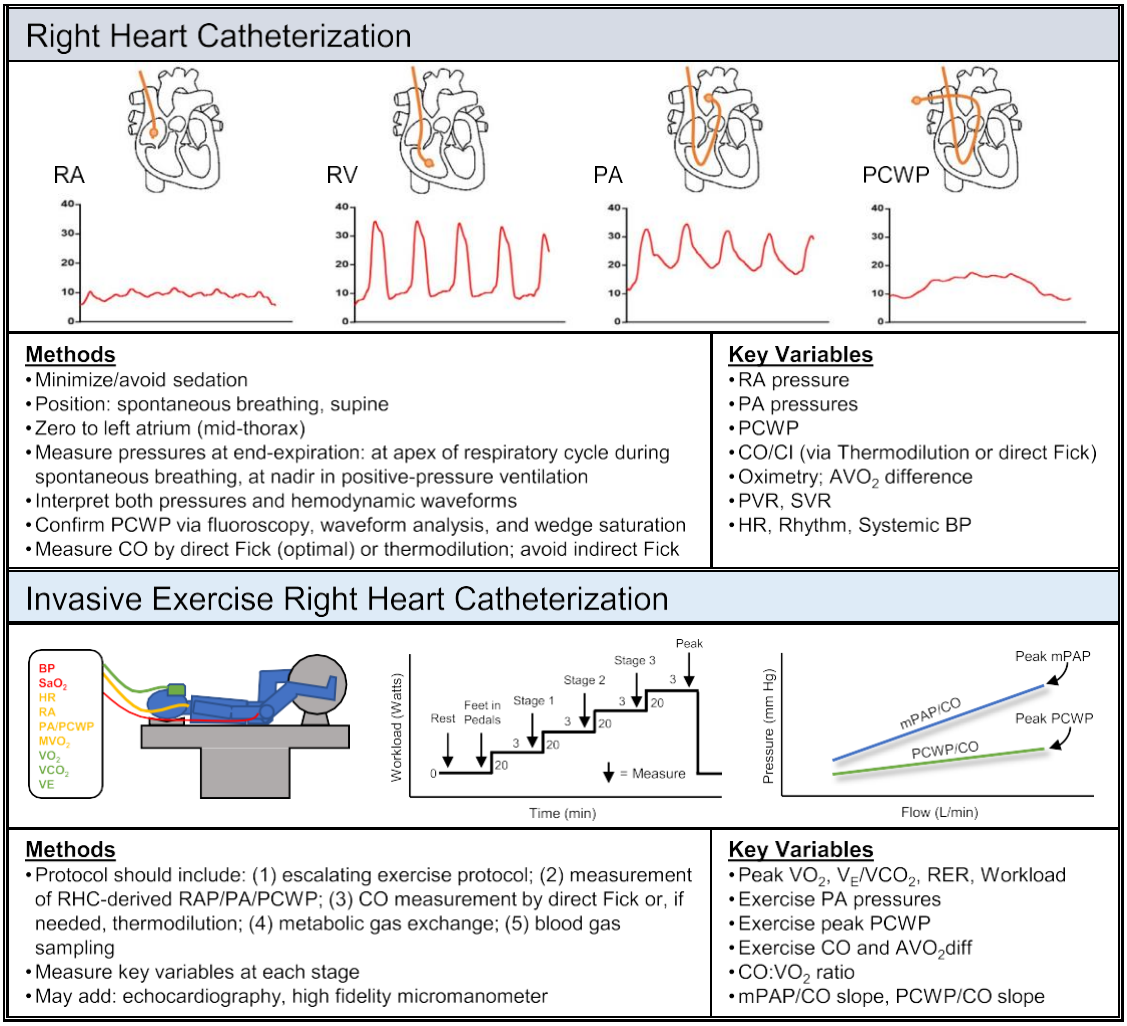

Fig. 2. Resting and invasive exercise right heart catheterization (RHC). Typical RHC tracings, exercise protocol schematics, key methods, and variables outlined for both. AVO_2, arteriovenous oxygen difference; BP, blood pressure; CI, cardiac index; CO, cardiac output; HR, heart rate; MVO_2, mixed venous oxygen saturation; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RER, respiratory exchange ratio; SaO_2, oxygen saturation; SVR, systemic vascular resistance; VE, pulmonary ventilation during exercise; VCO_2, rate of elimination of carbon dioxide; VO_2, venous oxygen saturation. Other abbreviations as in Fig. 1.

incompetence further limits CO reserve.[23,24] Depression in peak VO_2 is also related to a blunted augmentation of the AVO_2-diff.[25] Recent studies have further shown that greater increases in stressed blood volume during exercise further tax the heart–lung unit during exercise to increase the PCWP in HFpEF, owing to the decrease in venous capacitance.[26] Thus, multiple highly integrated mechanisms contribute to the hemodynamic derangements that develop during exercise in patients with HF.

Hemodynamic Assessment in the Catheterization Laboratory

Resting Hemodynamic Assessment

Right heart catheterization (RHC) is ideally performed with minimal conscious sedation in supine patients, often without interrupting anticoagulation, which is important in vulnerable populations such as in patients with an LVAD. The pressure transducer should be zeroed at the mid thorax (level of the left atrium).[27] Overdampening or underdampening of pressure tracings should be addressed through good technique, including aspiration and catheter flushing. Pressure measurements in each chamber are determined at end-expiration in the spontaneously breathing, quiet patient, taking the mean of 3 or more beats (Fig. 2). Note that, at end-expiration, the pressure is measured near the maximum value in the spontaneously breathing patient, which avoids the impact of negative pleural pressures; by contrast, pressure is measured at the minimum value in the mechanically ventilated patient to account for the impact of positive pleural pressure.[28]

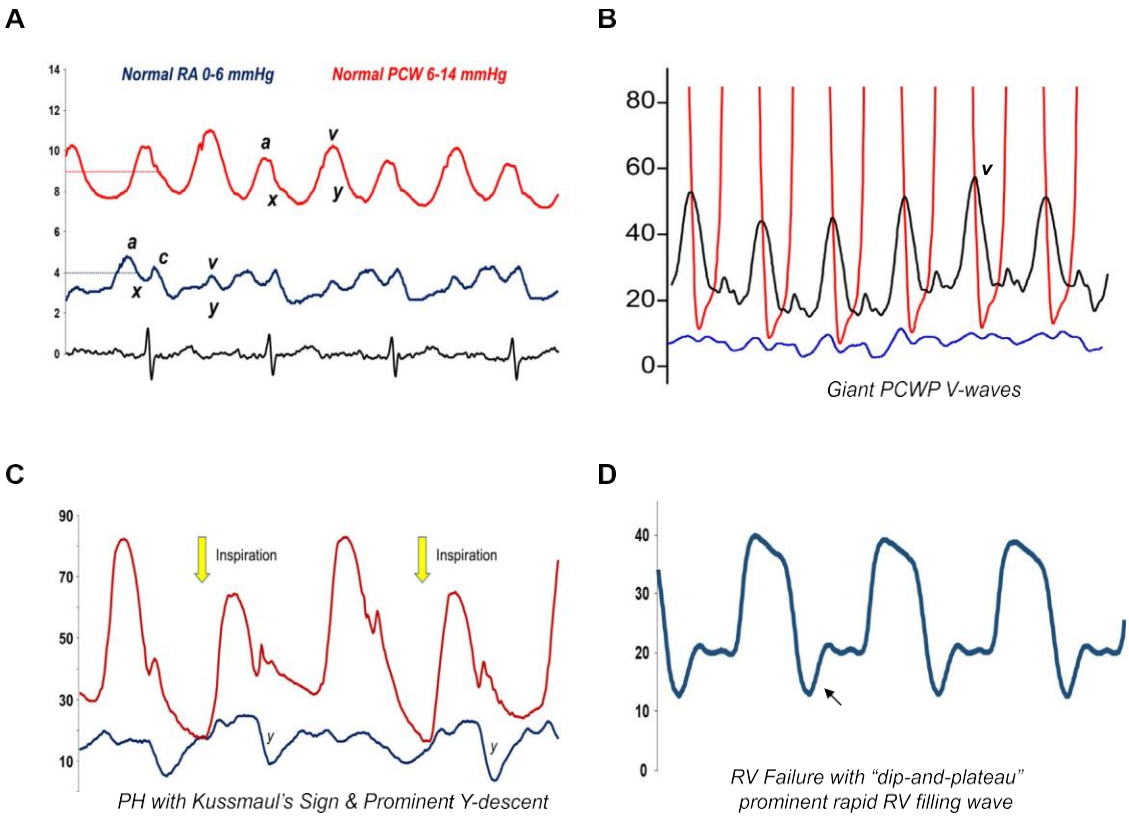

Fig. 3. Example hemodynamic tracings. Key points highlighted alongside tracings. (A) Normal RA and pulmonary capillary wedge tracings and values. (B) Giant V-waves on PCW tracing owing to decrease left atrial compliance. Care should go toward identifying mean PCW pressure by bisecting the A-wave (and not the V-wave) at end-expiration. (C) Pulmonary hypertension with prominent Y-descents and Kussmaul's sign (increase in RA pressure) with inspiration, collectively indicative of poor pulmonary vascular and RV compliance. (D) RV failure with a dip-and-plateau sign during diastole, indicative of severe RV dysfunction and diastolic pressure overload. The same can also be seen in constrictive pericarditis and restrictive cardiomyopathies when ventricular filling must occur early and rapidly owing to poor ventricular compliance. Abbreviations as in Figs. 1 and 2.

Care should be devoted to confirming the PCWP using fluoroscopy, waveform analysis, and pulmonary capillary wedge saturation.[29] The mean right and left atrial pressures are taken at mid a-wave. The PCWP tracing provides an estimate of left atrial pressure, which may differ from the LVEDP in patients with mitral valve disease or increased atrial stiffening. In addition to pressure amplitude, characteristics of hemodynamic waveforms reveal important diagnostic findings (Fig. 3 and Table 2).

CO is most accurately measured via the direct Fick method, where VO_2 is directly measured and divided by the difference in arterial and mixed venous (PA) oxygen content (AVO_2-diff). If the VO_2 cannot be measured, thermodilution is preferred because of inaccuracies in estimating indirect VO_2.[30] Although thermodilution is perceived to be inaccurate in cases of low output or tricuspid regurgitation, reasonable measurements are observed even in these settings.[31]

Table 2. Causes of Prominent or Blunted Hemodynamic Tracing Features

Tracing	Prominent	Blunted/Absent
V wave	Valve insufficiency; #atrial compliance; "atrial volume	—
A wave	Atrioventricular dyssynchrony; strong atrial contraction plus stiff ventricle or valve stenosis	Atrial fibrillation
Y descent	Valve insufficiency; restrictive/constrictive disease	Tamponade; valve stenosis

Oximetry plays a vital diagnostic role. A significant step-up in oxyhemoglobin saturation (2:8%) between the superior vena cava and the PA should prompt a full saturation run (with sampling from the superior and inferior vena cava, RA, RV, PA, and PA wedge position) to characterize a potential left-to-right shunt. The precise location of the step-up can help to localize the shunt. Values also help to quantify shunt severity by calculating the Q_p/Q_s, or the ratio of pulmonary-to-systemic flow. According to the Fick principle, $Q_p/Q_s = (SAO_2 - \text{Mixed venous } O_2)/(PCW\ O_2 - PA\ O_2)$, where the mixed venous O_2 is taken before the step-up (estimated as 0.75 [superior vena cava O_2] + 0.25 [inferior vena cava O_2]) if the step up is at the level of the RA). The Q_p/Q_s ratio is normally 1:1. A Q_p/Q_s ratio of greater than 1:1

Table 3. Invasive Hemodynamic Guidance in Common Clinical Scenarios

Scenarios	BP	HR	RAP	PCWP	CO	SVR	Potential Action
Dyspnea and unclear volume status	-	-	-	-	-	-	Workup lung disease, noncardiac dyspnea
	-	-	"	""	-	-	Diuresis
	-	-	""	-/#	-/#	-/"	Workup for PH, PE, pericardial disease, RV MI
Unclear volume status, perfusion, vascular resistance	-	-/"	-/#	-/#	-/#	-	Stop acute decongestion
	-/"	-/"	""	""	#	""	Diuresis + Vasodilator*
Worsening renal function during decongestion							Diurese to goal RAP (<8 mm Hg), PCWP (<15 mm Hg); vasodilate to decrease SVR (1000–1200 dynes/s/cm^{-5}) while maintaining MAP (65–70 mm Hg) - Sacubitril/valsartan oral - Hydralazine-isosorbide dinitrate oral - Nitroprusside IV (0.25–5.00 mg/kg/min[γ]
	#	"	""	""	#	-/"	Inotrope* Inotropes to increase cardiac index (>2.0 L/min/m^2) and MAP (>65 mm Hg): - Dobutamine (2.5–10.0 mg/kg/min) - Milrinone (0.125–0.500 mg/kg/min)
Hypotension of unclear etiology	##	"	-/#	-/#	#	""	Hypovolemic shock likely. Treat with IV fluid or blood, depending on cause.
	##	"	-	-	-/"	##	Distributive shock likely. Treat with IV fluid + vasopressor, workup etiology. Vasopressors to consider: - Norepinephrine (0.01–2.00 mg/kg/min) - Vasopressin (0.04 U/min)
	##	"	""	""	##	#/"	Cardiogenic shock likely. Inotrope/vasopressor § temporary MCS, workup etiology. If hypotension severe, consider vasopressors: - Epinephrine (0.01–0.10 mg/kg/min) - Norepinephrine (0.01–2.00 mg/kg/min)

*In general, vasodilator-based therapy is preferred if BP allows (eg, MAP >65 mm Hg) given the increases in myocardial O2 demand and proarrhythmia associated with inotropes.

[γ]IV nitroprusside is monitored with invasive BP monitoring, then gradually transitioned to oral vasodilator therapy once desired hemodynamic effects have been achieved.BP, blood pressure; HR, heart rate; IV, intravenous; MCS, mechanical circulator support; MI, myocardial infarction; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; RAP, right atrial pressure; RV, right ventricle; SVR, systemic vascular resistance. Other abbreviations as in Table 1.

indicates net left-to-right shunting, with ratios of more than 1.5 to 2.0 considered significant.[32]

Invasive Hemodynamic Exercise Testing

Invasive hemodynamic exercise testing affords the ability to identify each of the hemodynamic abnormalities of exercise, making it the gold standard to differentiate various causes of exertional dyspnea, including HFpEF, exercise-induced PH, dynamic valvular insufficiency, preload failure, and peripheral limitations/mitochondrial disease (Table 1). Protocols differ slightly across centers,[11,29,33] but should include (1) an escalating exercise workload in the supine or upright position, (2) simultaneous measurements of RAP, PA, and PCWP, (3) CO measurement using either direct Fick or thermodilution, (4) measurement of gas exchange using a metabolic cart (if available), and (5) assessment of arterial and venous O_2 content (Fig. 2).[11,29,33] Controversies exist as to whether pressures should be measured at end-expiration or using the mean of respiratory cycle; clearly reporting both values is probably ideal. Additional evaluation may be added, depending on the clinical question, including concomitant echocardiographic assessment (eg, valvular disease). Some laboratories use a high-fidelity micromanometer advanced through the fluid-filled catheter to provide more precise pressure waveform data during exercise, where fluid-filled catheters are less accurate.[29]

Specific Disease States

HF With Reduced EF

Most clinical decisions in HFrEF can be made based on history, physical exam, and laboratory findings. In fact, the Heart Failure Society of America guidelines recommend against the routine assessment of invasive hemodynamics in HF.[34] These guidelines are supported by the seminal Evaluation Study of Congestive heart failure and Pulmonary artery catheterization Effectiveness (ESCAPE) trial,[35] which found no mortality benefit to routine PA catheter use in acute decompensated HF.

Hemodynamic assessments, however, do provide actionable data in more challenging patients with HF in whom either volume or perfusion status remains unclear (Table 3).[34] This finding is congruent with more recent data suggesting that PA catheter use improves outcomes in advanced HF or CS.[36,37] Fig. 4 outlines the evolution of hemodynamic indices in the context of HFrEF disease progression. Invasive

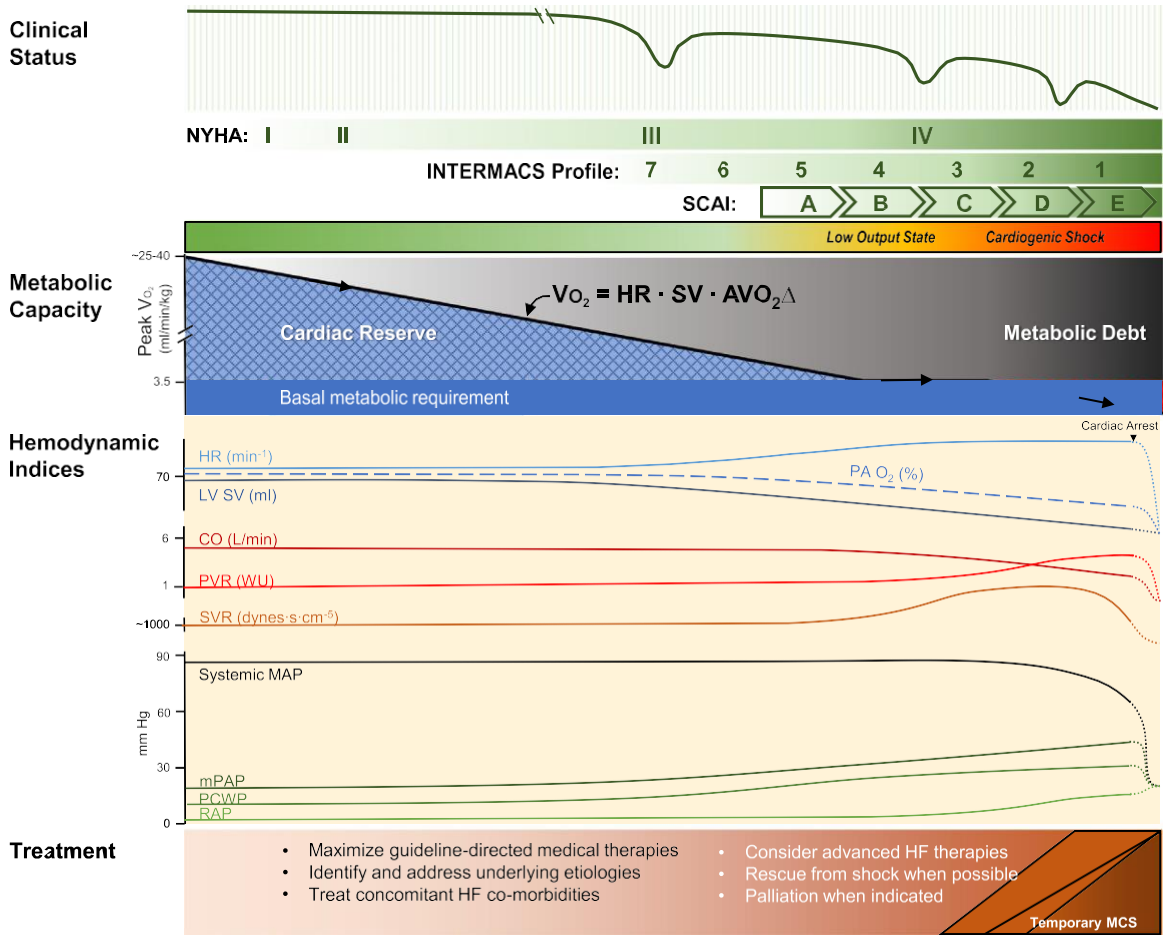

Fig. 4. Hemodynamic indices in HF and cardiogenic shock (CS). As HF progresses, metabolic capacity gradually wanes. Patients first suffer the loss of cardiac reserve, but maintain normal rest perfusion. Multiple hemodynamic indices continuously adapt to gradually waning stroke volume (SV) to maintain CO and BP. Cardiac pressures increase as the heart fails to maintain normal filling; pulmonary pressures increase too. As reserve fades, small perturbations in the metabolic supply–demand balance can precipitate exacerbation. In later disease, multiple compensatory mechanisms fail, leading to low output and cardiogenic shock states. Upon cardiac arrest, flow stops and pressures converge on the mean circulatory filling pressure. Treatments throughout are directed toward the clinical and hemodynamic state. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support Profiles; NYHA, New York Heart Association; SCAI, Society for Cardiovascular Angiography & Interventions Classification of Cardiogenic Shock. Other abbreviations as in Figs. 1 and 2.

hemodynamic assessment may be more helpful in the more advanced stages of HFrEF, including patients in whom an occult low output state may be present, when advanced therapies are being considered, and in acutely ill patients with hypotension (Fig. 4).

Cardiogenic Shock

CS occurs when there is a primary myocardial insult that decreases CO to a level insufficient to maintain end-organ perfusion and results in pulmonary and/or venous congestion from increased cardiac filling pressures.[17] The rapidity by which CO decreases is important, because clinical manifestations may not be apparent if the decrease is gradual. Sudden impairment of CO is usually poorly tolerated and results in pallor, cold extremities, and mental status changes; congestion is manifest by tachypnea and hypoxemia. By contrast, the same magnitude of hemodynamic abnormalities that evolves over weeks to months in chronic HF may not be clinically apparent until a tipping point is reached.

Hypotension is the predominant hemodynamic manifestation of CS; in fact, the diagnosis is rarely considered unless hypotension is present. Most clinical investigations have used 90 mm Hg for systolic BP and 60 mm Hg for the mean arterial pressure for at least 30 minutes. The concomitant presence of hypoperfusion is required, assessed by examination[38] or simple measures of hypoperfusion, such as decreased urine output or increased lactate levels. It should be recognized that tissue hypoperfusion can be present without hypotension if CO has significantly decreased but endogenous vasoconstrictor responses are maintaining the BP.[39]

Table 4. SCAI Grading System of Cardiogenic Shock

Stage	Description	Bedside Findings	Biochemistry	Hemodynamics
A: At risk	At risk for development of CS; includes MI and patients with HF	Normal JVP; lungs clear; warm and well perfused	Normal renal function; Normal lactate	Normotensive; CI >2.5, CVP <10, PA sat >65%
B: Beginning CS	Clinical evidence of relative hypotension or tachycardia, without hypoperfusion	Increased JVP; rales; warm and well perfused	Normal lactate; mild renal impairment; increased BNP	SBP <90 or MAP <60 or >30 mm Hg decrease, pulse >100; CI >2.2, PA sat >65%
C: Classic CS	Hypotension and hypoperfusion requiring an intervention (inotrope, pressor, or MCS)	May look unwell, ashen; rales, assisted ventilation; cold, clammy, low urine output	Increased lactate; Creatinine worsening; Increased liver chemistries; increased BNP	SBP <90 or MAP <60 or >30 mm Hg decrease; CI <2.2, PCWP >15, RAP/PCWP >0.8, PAPi <1.85, CPO <0.6
D: Deteriorating	A category C patient who is getting worse; failing first interventions	Any of stage C	Any of stage C and deteriorating	Any of stage C despite multiple pressors or additional MCS devices
E: Extremis	Cardiac arrest with ongoing CPR and/or ECMO; requiring multiple interventions	Near pulselessness cardiac collapse; mechanical ventilation; defibrillator use	Any of above and pH <7.2 Lactate >5	No SBP without resuscitation; PEA or VT/VF; hypotension despite max support

BNP, B-type natriuretic peptide; CI, cardiac index; CPO, cardiac power output; CPR, cardiopulmonary resuscitation; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; JVP, jugular venous pressure; PA sat, pulmonary arterial saturation; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia. Other abbreviations as in Tables 1 and 3.

In 2020, the Society for Cardiovascular Angiography & Interventions Clinical Expert Consensus Statement on the Classification of CS[40] leveraged an integrated diagnostic approach using both clinical assessment and invasive hemodynamics to define the CS syndrome as well as its severity across five temporal stages (Table 4). Recent data from the Cardiogenic Shock Working Group registry have revealed that this scheme has prognostic value in CS—particularly increases in central venous pressure, which reflect pericardial restraint and biventricular HF.[41] Other indices have been used to provide a more composite quantitative picture of shock. LV cardiac power output (CPO) is the product of the CO and mean arterial pressure divided by 451. A decrease in cardiac power may be a consideration for the use of intra-aortic balloon pump counterpulsation, because a low LV CPO is associated with poor hemodynamic stabilization in patients with advanced HF treated with intra-aortic balloon pump counterpulsation.[6] However, neither CPO nor the cardiac index were predictive of shock severity or mortality in the Cardiogenic Shock Working Group registry.[41] A limitation of the commonly calculated CPO is the absence of the RAP in the formula, which had been part of its original derivation.[42]

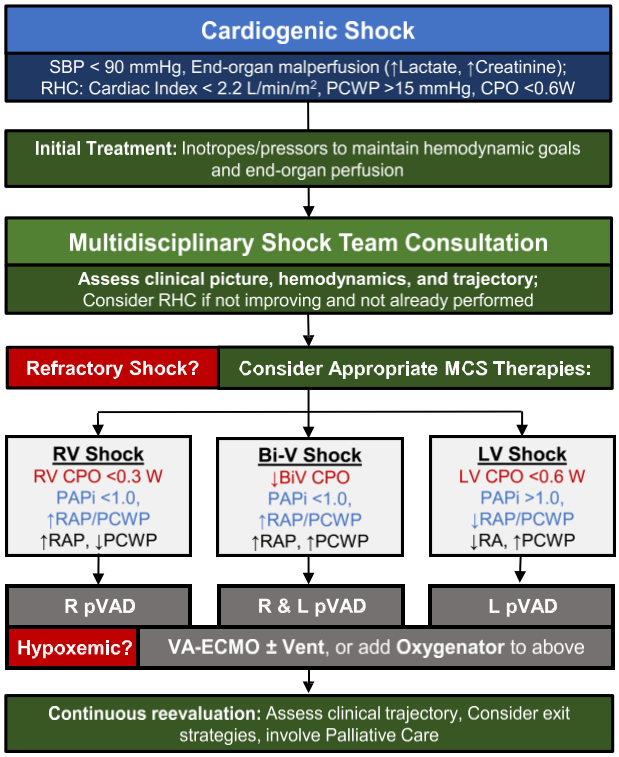

Fig. 5. A proposed team-based approach to the management of refractory CS. LV cardiac power output (CPO), LV cardiac power output (MAP¢CO/451); RV CPO (mPAP¢CO/451); PAPi, pulmonary artery pulsatility index ((sPAP-dPAP)/RAP); RAP/PCWP, right atrial pressure-to-pulmonary capillary wedge pressure ratio; pVAD, percutaneous ventricular assist device. Other abbreviations as in Figs. 1 and 2.

Hemodynamic phenotyping of CS has value in guiding therapeutic strategies to support the circulation[43–45] until either recovery or more durable circulatory support (eg, transplantation or LVAD). Proposed phenotyping algorithms[43–45] generally rely on CPO, PA pulsatility index (to assess the right heart), and filling pressures to guide management (Fig. 5). However, the criteria for escalation to temporary mechanical circulatory support despite pharmacologic support for CS are not clear and, in general, are circumstantially driven by patient characteristics as well as center and provider

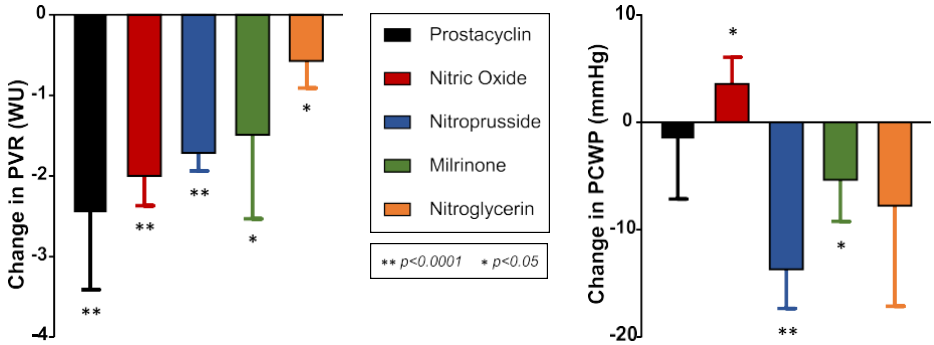

Fig. 6. Average effect on PVR and PCWP of select provocative agents useful for vasodilator testing of precapillary pulmonary hypertension.[49] SBP, systolic blood pressure. Other abbreviations as in Figs. 2 and 5.

expertise. Introducing mechanical circulatory support to pharmacologic support may be able to prevent the hemometabolic consequences of CS.[46] Hemometabolic shock constitutes the final and most mortal phase of shock; once manifest alongside congestion and malperfusion, decreasing systemic vascular resistance owing to vascular exhaustion leads to profound hypotension (Fig. 4) and particularly poor outcomes. Although lactate is often measured and is associated with outcomes, it has been difficult to show that decreasing lactate through either pharmacologic or mechanical means improves outcomes.

The authors recommend prompt confirmation of the putative diagnosis of CS with invasive hemodynamic data, followed by team-based management in an appropriate intensive care setting. Several large observational series suggest that PA catheterization use may be associated with improved outcomes in patients with CS,[28,36,37,41] but prospective randomized data do not yet exist and several practical issues limit its widespread adoption in routine clinical practice.

Hemodynamics in Heart Transplant and LVAD

Invasive hemodynamics play an integral role in HFrEF patients being considered for advanced surgical therapies. When considering heart transplantation, fixed precapillary PH (pulmonary vascular resistance [PVR] >3.5–5.0 Wood units [WU]) is a relative contraindication, because transplanting an allograft naïve to high pulmonary pressures can precipitate acute right HF and death.[47] In these patients, a provocative challenge with intravenous sodium nitroprusside can identify lungs with "reversible" precapillary PH still amenable to heart transplantation. If patients with a baseline PVR of more than 2.5 WU treated with nitroprusside decrease to 2.5 WU or less without systemic hypotension, their post-transplant risk profile is similar to those with a baseline PVR of 2.5 WU or less.[48] Other provocative agents such as milrinone and prostacyclin, each with their own anticipated effect on PVR and PCWP (Fig. 6), have also been studied prospectively.[49]

Although infrequently used for this purpose, invasive exercise testing can also help evaluate transplant appropriateness. By measuring both supply (CO) and demand (VO_2) in tandem, one can directly assess the ability of the heart to match metabolic requirements during exercise. CO reserve limitation is defined by a supply–demand ratio that is less than 80% of expected ($DCO:DVO_2 < 4.8:1$). Noninvasive cardiopulmonary exercise testing is more often used to assess transplant candidacy and estimate CO reserve, but it must be remembered that 50% of the variability in the peak VO_2 is explained by the AVO_2-diff, which is not measured during noninvasive cardiopulmonary exercise testing. Patients with a low peak VO_2 but a normal CO reserve may respond better to exercise training to improve peripheral reserve, rather than undergoing transplantation or LVAD implantation. Indeed, Chomsky and colleagues[50] showed that impairments in CO reserve were far more prognostic than peak VO_2 in patients with advanced HFrEF undergoing transplant evaluation. Additionally, some patients with HF may have relatively normal CO at rest, but virtually no CO reserve with exertion; these patients may also benefit from transplantation.

Hemodynamics are equally important when considering durable LVADs. Early right-sided HF (RHF) after LVAD implantation remains a relatively common cause of post-LVAD morbidity and mortality, occurring in 9%–42% of cases.[51] Numerous models have been developed to predict post-operative early RHF, but none has proven to have high discrimination, Some hemodynamic indices have emerged to be more useful: Kussmaul's sign,[52] preoperative RAP (>15 mm Hg), increased RAP/PCWP ratio (>0.54–0.63), decreased RV stroke work index (<0.25 mm Hg¢L/m^2), tachycardia, and low cardiac index (<2.2 L/min/m^2) have predicted RHF risk across multiple models.[51] Decreased PA pulsatility index (PA pulsatility index = [PASP–PADP]/RAP) has also shown

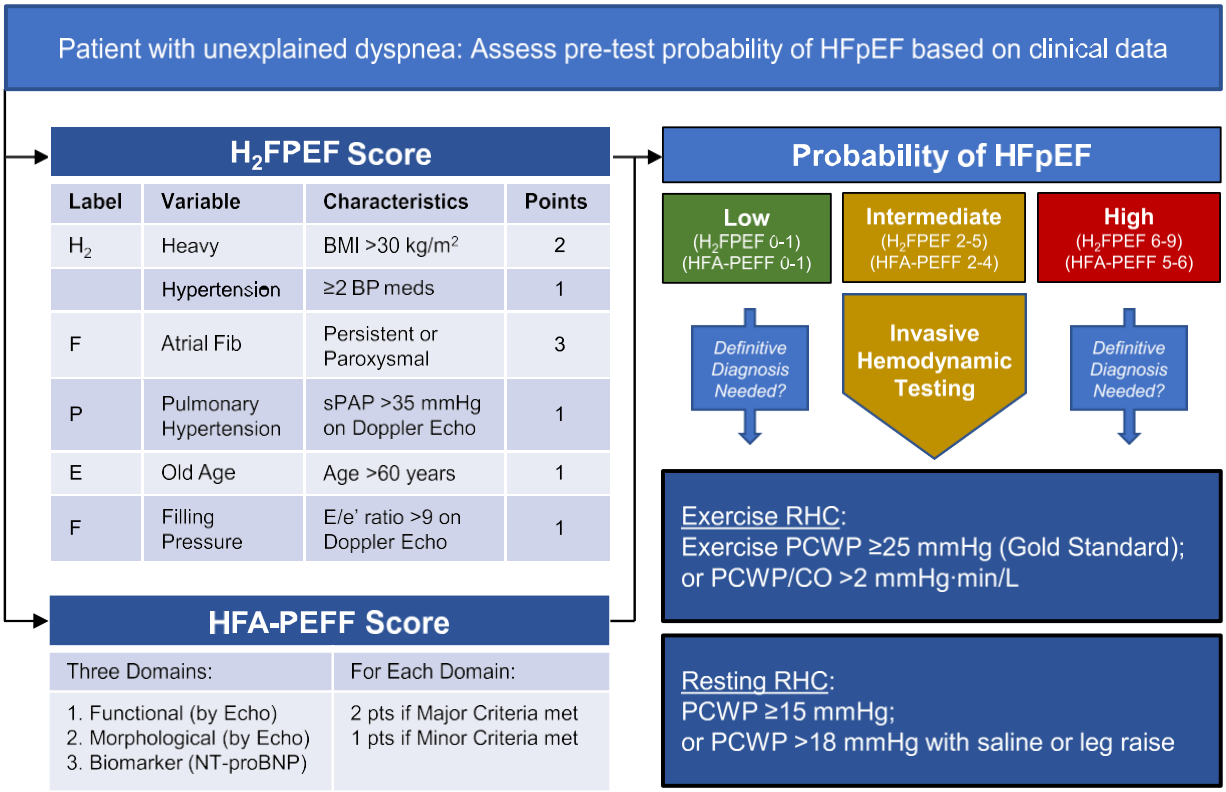

Fig. 7. A diagnostic approach to HFpEF. Patients with unexplained dyspnea can be assessed by the H_2FPEF score, or an alternative HFA-PEFF score. Those with intermediate probability, or others if needed, can be further evaluated using invasive hemodynamic exercise testing (gold standard), or PA catheterization at rest with provocative maneuvers. Abbreviations as in Fig. 1.

predictive capability.[53,54] These hemodynamic predictors are complemented by clinical, echocardiographic, and laboratory risk markers of RHF, such as patient acuity, severe RV contractile dysfunction, and an increased blood urea nitrogen.[51] An integrated right heart assessment—incorporating clinical, imaging, and hemodynamic predictors of RHF—along with careful monitoring and early treatment of RHF, are well advised in the consideration and execution of LVAD surgery.

Hemodynamics also play a crucial role in managing patients after LVAD implantation. When needed, hemodynamics enable precise assessments of CO, filling pressures, and afterload, which all significantly affect the very afterload-sensitive flow of blood through an LVAD (in particular the centrifugal continuous flow LVAD). Hemodynamics, when added to echocardiography, also improve diagnostic accuracy when considering LVAD complications such as pump thrombosis, because pump compromise may manifest in LV pressure and CO changes not apparent on imaging.[55] PA catheterization also plays an important role in LVAD speed optimization, because as many as 40% of patients with an LVAD have suboptimal RAP and PCWP, even after clinical/echocardiographic-based optimization.[56] Hemodynamic-guided ramp studies, during which both RHC and echo measurements are repeated after successive LVAD speed increases, can improve filling pressure optimization,[56] direct subsequent medical interventions, and potentially decrease HF hospitalizations,[57] although further prospective study is required. PA catheterization also monitors for precapillary PH in bridge-to-transplant LVAD patients. Last, invasive hemodynamic exercise testing has also been used in LVAD recipients. Current generation LVADs maintain a static speed, which limits CO reserve[58] and peak VO_2,[59] and invasive exercise testing may allow for more refined estimates of the ideal LVAD speed that optimizes both resting and exercise flow.

HF With Preserved EF

More than one-half of patients with HF suffer from HFpEF.[60] Overt HFpEF can be diagnosed when the clinical syndrome occurs in conjunction with preserved LV EF and clear noninvasive evidence of congestion and diastolic dysfunction.[61] Natriuretic peptide levels are helpful if increased, but often are not.[60] Thus, noninvasive diagnostic criteria applied at rest miss a large proportion of HFpEF patients who develop elevations in cardiac filling pressures exclusively during exercise.[1] This

is because long before abnormalities manifest at rest, the left heart in HFpEF loses its ability to maintain low filling pressures while trying to meet the increased demands of exercise.

Owing to the poor sensitivity of clinical and noninvasive diagnostics, invasive hemodynamic testing plays a major role in the optimal evaluation of HFpEF.[60] For the patient with overt HFpEF, RHC can readily diagnose increased left-sided filling pressures at rest while concurrently ruling out World Society of Pulmonary Hypertension (WSPH) group I PH. If indicated, endomyocardial biopsy performed at time of RHC can rule out cardiac amyloidosis. Hemodynamics are even more useful during exercise testing in HFpEF, because the variables that define HF are directly measured. HFpEF is defined invasively during supine exercise as a peak exercise PCWP of 25 mm Hg or greater,[1] which is the current definition endorsed by diagnostic guidelines.[62] A complementary hemodynamic pattern indicative of HFpEF involves measuring PCWP as a function of CO at regular intervals during exercise. A PCWP/CO slope of more than 2 mm Hg¢min¢L^{-1} has been shown to be predictive of outcomes.[33] Invasive exercise testing also allows assessment of CO reserve, which as outlined earlier, can help to confirm cardiac limitation as the cause of exertional dyspnea.

Invasive exercise testing requires operator expertise, time, and capital investment. Alternative approaches include saline loading, leg raise hemodynamics, and exercise echocardiography. Saline loading is simpler to perform,[63] but still involves catheterization and its sensitivity is inferior to exercise testing.[64] An increase in the PCWP with a passive leg raise has been shown to provide good discrimination of HFpEF from noncardiac dyspnea, but provides less physiologic information.[1] Exercise echocardiography shows promise as a noninvasive method, but although some investigators have shown its diagnostic accuracy,[65] others have not.[66]

To help inform decision-making regarding invasive testing, we advocate for an integrated, stepped diagnostic approach to the work-up of HFpEF (Fig. 7). Recently, Reddy and colleagues[67] derived and then validated a simple diagnostic model to estimate the pretest probability of HFpEF, termed the H_2FPEF score (Fig. 7). The H_2FPEF score exhibits robust discrimination of HFpEF from noncardiac etiologies of dyspnea (area under the curve 0.841, $P < 0.0001$).[67] The use of this clinical score allows for a Bayesian approach to the HFpEF diagnosis, whereby those with low and high probability can be ruled out and in, respectively, while those with intermediate probability (score 2–5) can go on to invasive hemodynamic exercise testing (Fig. 7).[60] An alternative score put forth by the European Society of Cardiology called the HFA-PEFF score is somewhat more complicated but can be used as an alternative or complementary approach (Fig. 7).[62]

Pulmonary Hypertension

PH was defined for nearly 50 years as a mPAP of 25 mm Hg or higher,[68] but recent studies have shown that normal mPAP is actually 14.0 § 3.3 mm Hg,[69] and several studies have revealed that mPAP in the 21–24 mm Hg range confers increased mortality.[68,70] Accordingly, the latest WSPH proposed lowering the threshold of PH to a mPAP of more than 20 mm Hg.[68] However, to diagnose group 1 PH (precapillary or pulmonary arterial hypertension, PAH), a PVR of 3 or more WU and a PCWP of less than 15 mm Hg must also be present.[68] Once PAH is diagnosed, vasoreactivity testing should be performed in patients with idiopathic, heritable, or anorexigen-associated PAH, because in these cases vasoreactivity influences prognosis and treatment.[71] Testing is performed by administering inhaled nitric oxide (or alternatives like intravenous epoprostenol), with vasoreactivity present if the mPAP decreases by more than 10 mm Hg to less than 40 mm Hg without a decrease in CO.[72]

Group 2 PH is diagnosed when the mPAP is greater than 20 mm Hg and the PCWP is 15 mm Hg or higher and is seen in at least 50%–80% of patients.[73] Group 2 PH may be subcategorized as isolated post-capillary PH when the PVR is less than 3 WU, or combined precapillary and post-capillary PH when the PVR is 3.0 or more WU, where the mPAP is increased out of proportion to left heart disease.[73] Patients in the latter group display a distinct hemodynamic profile characterized by greater RV dysfunction, ventricular interdependence, more severe exercise limitation, and a greater risk of death.[74-76] Not surprisingly, hemodynamic indices that reflect RHF—including an increased RAP, decreased SV,[77] and Kussmaul's sign[78]—have been shown to predict poor functional capacity and outcomes, both in group 2 as well as group 1 PH. PVR is related to PA compliance (SV/PA pulse pressure) in a hyperbolic fashion, wherein patients with early stages of PA vascular disease (slight increases in PVR) develop marked reductions in compliance with further progression. Increases in the PCWP further depress PA compliance at any given PVR.[79] Like increases in PVR, decreases in PA compliance are highly prognostic in group 2 PH.[75]

Distinguishing group 1 from group 2 PH is of crucial therapeutic importance, because there are multiple effective treatments for the former but no proven direct therapies for the latter.[80] The lynchpin for this distinction relies on accurate assessment of PCWP. Here, the wedge saturation may be particularly useful. Indeed, a recent study showed routine

wedge saturation measurements reclassified WSPH grouping in 11.8% of patients when compared with diagnoses based on PCWP measured without saturation assessment.[81]

Invasive hemodynamic exercise testing may also play a role in PH. Exercise-induced PH (EiPH) was formerly defined by an exercise mPAP of greater than 30 mm Hg, but in 2008 this criterion was removed from the guidelines.[68] Ongoing efforts exist to define EiPH because earlier identification and treatment of PH hold promise to improve outcomes, although further study is required. Two criteria have been proposed. One defines EiPH as an exercise mPAP/CO slope of greater than 3 mm Hg¢min¢L^{-1},[82] whereas another defines EiPH when both the mPAP is greater tan 30 mm Hg and the total pulmonary resistance (mPAP/CO) is more than 3 WU at exercise peak.[83] To distinguish exercise-induced pulmonary vascular disease from HFpEF, measurements of PCWP during exercise are necessary.[1,33] Recent studies have revealed that patients with EiPH display poorer clinical outcomes,[33,84] and emerging data suggest it may represent a therapeutic target. One recent trial showed that the b-agonist albuterol improved pulmonary vascular reserve with exercise (lower PVR and mPAP/CO slope) as compared with placebo.[85] Further study is required with longer durations of treatment in multicenter trials to determine if these hemodynamic improvements translate to clinical improvement.

Other Indications

Invasive hemodynamic assessments are often helpful in patients with valvular heart disease whenever discrepancies exist between the clinical picture and noninvasive assessment of valve severity (eg, low-flow, low-gradient aortic stenosis or combined mitral stenosis and HFpEF).[86]

They may also be useful in adult congenital heart disease to diagnose shunts or assess PH, or in more complex diseases, including Fontan physiology. For example, in adults with the Fontan palliation, an increased mPAP/CO slope with exercise is associated with more end-organ dysfunction and abnormal flow-mediated vasodilation, suggesting that this factor may provide means to stratify patients for vasodilator administration.[87]

Invasive assessment is often helpful to make the diagnosis of high output HF and may also allow for determination of etiologies, such as intracardiac or systemic shunts.[88] Exercise RHC testing can also diagnose preload insufficiency, where peak VO_2 is depressed owing to low depressed DCO/DVO_2 in tandem with low to normal filling pressures, as well as peripheral limitations, where it is depressed because of low AVO_2-diff, with normal CO reserve.[16,29]

Last, invasive hemodynamics play a crucial role in distinguishing constrictive pericarditis from primary myocardial disease. Both disorders are characterized by increased right- and left-sided filling pressures with steep Y-descents, a frequently positive Kussmaul sign, and a dip-and-plateau sign in the ventricles. However, simultaneous comparison of RV–LV and LV–PCWP pressure tracings can distinguish myocardial from pericardial disease.[89] In constriction, LV and RV systolic pressure changes during respiration are discordant, or 180° out of phase with one another, owing to enhanced ventricular interdependence. In restrictive myocardial disease, LV and RV pressures change in phase. In constriction, there is also intrathoracic–intracardiac dissociation, where the mean pressure gradient between PCWP and LV during diastole decreases by 5 mm Hg or more.

Conclusions

After years of dormancy, the value of invasive hemodynamics has re-emerged front and center, playing a crucial role in the scope of the HF practice. A thorough understanding of the principles and practice of the hemodynamic assessment, along with a thoughtful application across the broad range of HF disease states are of vital importance to HF clinicians serving their patients. Future advances in the understanding and application of hemodynamics will only further cement their central role in the care of patients with HF.

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